Cardiac remodelling and functional alterations in mild-to-moderate renal dysfunction: comparison with healthy subjects

Anna M. Asp[1,2], Carin Wallquist[3,4], Anette Rickenlund[1,2], Britta Hylander[3], Stefan H. Jacobson[5], Kenneth Caidahl[1,2] and Maria J. Eriksson[1,2]

[1]Department of Clinical Physiology, Karolinska University Hospital, [2]Department of Molecular Medicine and Surgery, Karolinska Institutet, [3]Department of Nephrology, Karolinska University Hospital, Karolinska Institutet, Stockholm, [4]Division of Nephrology, Department of Medicine, Västmanlands Hospital, Västerås, and [5]Division of Nephrology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden

Summary

Correspondence

Anna M. Asp, Department of Clinical Physiology N2:01, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

E-mail: anna.mathilda.asp@gmail.com

Introduction Left ventricular (LV) hypertrophy (LVH) and reduced LV function correlate with poor prognosis in patients with chronic kidney disease (CKD). Our aim is to investigate whether mild-to-moderate CKD is associated with cardiac abnormalities.

Methods Echocardiography, including tissue Doppler imaging, was performed in 103 patients with CKD at stages 2–3 and 4–5, and in 53 healthy controls. The systolic (s') and diastolic myocardial velocity (e'), and the transmitral diastolic flow velocity (E) were measured, and E/e' was calculated.

Results Patients with chronic kidney disease had higher mean E/e' than controls (mean E/e': controls 5.00 ± 1.23 versus CKD 4–5 6.36 ± 1.71, P<0.001 and versus CKD 2–3 5.69 ± 1.47, P = 0.05), indicating altered diastolic function in the patients. The CKD groups showed lower longitudinal systolic function than controls, as assessed by atrio-ventricular plane displacement and s' (mean s': controls 11.5 ± 1.9 cm s^{-1} versus CKD 4–5 10.4 ± 2.1 cm s^{-1}, P = 0.03 and versus CKD 2–3 10.4 ± 2.1 cm s^{-1}, P = 0.02). The prevalence of LVH was higher in patients with CKD than in controls (controls 13% versus CKD 4–5 37%, P = 0.006 and versus CKD 2–3 30%, *P* = 0.03).

Conclusion Alterations in systolic and diastolic myocardial function can be seen in mild-to-moderate CKD compared with controls, indicating that cardiac involvement starts early in CKD, which may be a precursor of premature cardiac morbidity.

Introduction

Chronic kidney disease (CKD) is strongly associated with an increased risk of cardiovascular (CV) disease (CVD) and all-cause mortality (Foley *et al.*, 1998; Anavekar *et al.*, 2004; Go *et al.*, 2004). There is an independent, graded association between renal dysfunction and the risks of CVD and death (Anavekar *et al.*, 2004; Go *et al.*, 2004). However, studies investigating the association between mild renal insufficiency and CV risk have shown discordant results (Culleton *et al.*, 1999; Henry *et al.*, 2002; Anavekar *et al.*, 2004; Hosseinpanah *et al.*, 2012).

The increased CV risk in CKD is associated with cardiac remodelling, that is, left ventricular (LV) hypertrophy (LVH) (Foley *et al.*, 1995; Levin *et al.*, 1999; Middleton *et al.*, 2001; Zoccali *et al.*, 2004a). In a cohort of predialysis patients, LVH was the strongest predictor of progression to end-stage renal

disease (ESRD) or death (Paoletti *et al.*, 2011). Reduced kidney function is also a risk factor for the development of heart failure (Fried *et al.*, 2003; Kottgen *et al.*, 2007). The risk of CV events in ESRD has been found to be highest in patients with both LVH and reduced LV function (Zoccali *et al.*, 2004b). Although published data indicate an increasing prevalence of LVH with declining renal function (Levin *et al.*, 1999; Nardi *et al.*, 2009; Chen *et al.*, 2011; Matsumoto *et al.*, 2012), the results regarding early-stage kidney disease are conflicting (Henry *et al.*, 2005; Paoletti *et al.*, 2005). Also, data regarding the association between decline in renal function and LV function are discordant (de Almeida *et al.*, 2007; Edwards *et al.*, 2008; Nardi *et al.*, 2009; Hung *et al.*, 2010; Chen *et al.*, 2011; Liu *et al.*, 2011; Park *et al.*, 2012).

Tissue Doppler imaging (TDI) allows the quantitative evaluation of myocardial function. The technique has an advantage over conventional echocardiography in diagnosing subclinical

abnormalities in systolic and diastolic LV function (Vinereanu et al., 2001; Derumeaux et al., 2002). In advanced CKD, even subclinical signs of diastolic LV dysfunction are associated with worse prognosis (Rakhit et al., 2007; Dogan et al., 2012). Only few studies have evaluated systolic function in CKD using TDI (Hayashi et al., 2006; Edwards et al., 2008; Gulel et al., 2008; Liu et al., 2011).

The aim of our study was to evaluate cardiac structure and function in non-dialysis patients, with different stages of CKD, compared with healthy controls. We were particularly interested to determine whether mild-to-moderate CKD is associated with cardiac remodelling or myocardial dysfunction.

Methods

Patients and control subjects

One hundred three Swedish speaking, non-dialysis patients with CKD, 18–65 years of age, and 53 controls were included in a prospective single-centre observational cohort study, PROGRESS 2002 (Factors impacting progress of renal insufficiency). In the present study, we have analysed the baseline echocardiographic variables in the patients with CKD compared with controls.

Patients were recruited consecutively from the outpatient clinic at the Department of Renal Medicine at the Karolinska University Hospital during 2002–2009 if they had renal function corresponding to stages 2–3 (mild-to-moderate renal dysfunction) or stages 4–5 (severe renal dysfunction) CKD as defined by the National Kidney Foundation (NKF) (National Kidney Foundation, 2002). Patients with known current malignancy were excluded. The patients with CKD were divided into two groups according to glomerular filtration rate (GFR): 49 patients with stage 4–5 CKD (GFR $15 \cdot 3 \pm 3 \cdot 9$ ml min^{-1} per $1 \cdot 73$ m^2) and 54 patients with stage 2–3 CKD (GFR $60 \cdot 1 \pm 5 \cdot 2$ ml min^{-1} per $1 \cdot 73$ m^2). Fifty-three healthy controls (GFR $99 \cdot 4 \pm 12 \cdot 1$ ml min^{-1} per $1 \cdot 73$ m^2), matched for age and sex with the patients with stage 2–3 CKD, were recruited. Of these, 30 were randomly selected from the Swedish Total Population Register and 23 were recruited through the website of the regional university hospital. Interested subjects underwent an interview concerning their health history and medication. Inclusion criteria for the controls were absence of kidney disease, CVD, and diabetes and no ongoing medication.

Before their inclusion in the study, the GFR of all participants was measured by iohexol clearance (Krutzén et al., 1984). After inclusion, all participants underwent clinical investigation, laboratory testing and transthoracic echocardiography (TTE). Exclusion criteria for all participants included kidney transplantation, kidney donation or blood-transmitted disease. One included patient did not complete the baseline echocardiography and was excluded from this study together with her control subject. One of the controls was diagnosed with diabetes after inclusion and was then excluded; meaning that one of the patients with stage 2–3 CKD was without a matched control.

The study protocol was reviewed and approved by the Local Ethics Committee and Institutional Review Board of the Karolinska Institute at the Karolinska Hospital, and all participants gave their written informed consent.

Echocardiography

All ultrasound examinations were performed by two experienced sonographers using an ultrasound machine with a 4-MHz probe equipped with TDI capabilities (Sequoia 512; Siemens Medical Solutions, Mountain View, CA, USA). Two-dimensional, M-mode and Doppler echocardiography were acquired according to the guidelines of the American Society of Echocardiography (ASE) and stored digitally on magneto optical discs and on an EchoPAC server (Image Vault 5.0 system; General Electric Company, Horten, Norway). Heart rate was measured in the supine position during the echocardiography examination. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position after the TTE examination was completed.

Standard echocardiographic measurements from the parasternal long-axis view included LV end-diastolic internal dimension (LVIDd), end-diastolic interventricular septal wall thickness (SWTd), end-diastolic LV posterior wall thickness (PWTd) and left atrial end-systolic diameter (LADs). Relative wall thickness (RWT) was calculated as the sum of SWTd and PWTd divided by LVIDd. The mean wall thickness (MWT) of the septal and inferior wall was calculated. LV ejection fraction (LVEF) was calculated from M-mode recordings using the Teichholz method (Teichholz et al., 1976). LV mass (LVM) was obtained using M-mode in the standard parasternal long-axis view and calculated using the formula described by Devereux et al. and recommended by the ASE (Devereux et al., 1986; Lang et al., 2005). LV mass index (LVMI) was calculated as LVM/body surface area (BSA). LVH was defined as LVMI >95 g m^{-2} for women and >115 g m^{-2} for men, according to ASE recommendations (Lang et al., 2005). In those participants where M-mode images were not acquired in the parasternal long-axis view, LVEF, LVM and LVMI were calculated from 2D images. The measurements of LVEF, LVM and LVMI are presented as the mean of two cardiac cycles. The atrioventricular plane (AV-plane) displacement was measured from M-mode recordings at the mitral annulus adjacent to the anterior, septal, lateral and inferior LV wall using the regional values and the mean value of the four sites of AV-plane displacement of the mitral annulus (Höglund et al., 1988). The AV-plane displacement measurements are presented as the mean of three cardiac cycles.

Transmitral flow velocities were acquired with pulsed Doppler. The velocities of early transmitral diastolic flow velocity (E) and flow velocity during atrial contraction (A), their ratio (E/A ratio), E deceleration time and isovolumic relaxation time (IVRT) were measured. The transmitral

flow velocities are presented as the mean of two cardiac cycles.

Tissue Doppler imaging

After completion of the conventional echocardiography, pulsed tissue. Doppler imaging was performed. Early diastolic myocardial velocity (e'), late diastolic myocardial velocity (a') and peak systolic myocardial velocity (s') were obtained in the apical four-chamber view and the apical two-chamber view at the septal, lateral, inferior and anterior part of the mitral annulus. A 3-mm sampling volume was used. Mitral e' of the TDI recorded Doppler signal at the septal and lateral part of the mitral annulus was used to calculate the septal (E/e' sept) and lateral (E/e' lat) E/e' ratios. Both values and the mean E/e' ratio (the mean value of E/e' sept and E/e' lat) were used as estimates of the LV filling pressure. The mean of the s' velocities of the four sites was calculated. All TDI variables were measured by two experienced sonographers and are presented as the mean of three cardiac cycles.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0. (IBM Corp., Armonk, NY, USA). Results are presented as number, percentage, mean and standard deviation (SD). Group comparisons were performed using one-way analysis of variance (ANOVA), Tukey's *post hoc* test and chi-square test (χ^2) where applicable. A P value <0·05 for a two-tailed test was considered significant.

Results

The clinical characteristics of the study participants are summarized in Table 1. The mean age of the participants was 47·7 ± 11·0 years; 60% were men. There were no significant differences between the groups regarding age, sex or body size. There was a significant difference in SBP (P<0·001) and DBP (P = 0·04) only between patients with CKD stages 4–5 and controls.

Echocardiographic findings are summarized in Table 2 and Fig. 1. LVMI ranged from 91 ± 18 g m^{-2}, in the controls, to 107 ± 27 g m^{-2} in patients with CKD stages 4–5, and the difference was significant only between CKD 4–5 and controls (P = 0·006). However, there was a significantly higher prevalence of LVH in both CKD groups (CKD 4–5, 37%; CKD 2–3, 30%) compared with the controls (13%); CKD 4–5 versus controls P = 0·006, CKD 2–3 versus controls, P = 0·03. RWT and MWT were higher in the patients with CKD compared with controls, but the differences were significant only between CKD 4–5 and controls (P<0·001 for both RWT and MWT).

There were no significant differences between the groups regarding LV radial systolic function, assessed as LVEF calculated by Teichholz method. However, there was a tendency to higher LVEF in controls (66·0 ± 8·5%) compared with the

Table 1 Characteristics of the study population.

	Controls	CKD 2–3	CKD 4–5	P value	P value between groups (*post hoc*)
No. of patients	53	54	49		
Age (years)	47·4 ± 10·7	46·8 ± 10·8	49·1 ± 11·6	0·5	NA
Male	32 (60·4)	33 (61·1)	29 (59·2)	0·9[a]	NA
BMI	24·9 ± 3·5	25·7 ± 4·9	26·0 ± 4·2	0·4	NA
BSA (m^2)	1·92 ± 0·19	1·92 ± 0·24	1·91 ± 0·23	0·9	NA
Heart rate (beats min^{-1})	65·2 ± 10·0	64·9 ± 13·2	64·5 ± 12·5	0·9	NA
SBP (mmHg)	117 ± 12·4	123 ± 15·4	130 ± 19·8	<0·001	<0·001[b]
DBP (mmHg)	73 ± 8·9	77 ± 10·4	78 ± 10·3	0·03	0·04[b]
Diabetes	–	11 (20·4)	7 (14·3)	0·4[a]	NA
Diagnosis CKD					
Familial/hereditary/congenital diseases	–	14 (25·9)	13 (26·5)	0·9[a]	NA
Primary glomerulonephritis	–	17 (31·5)	12 (24·5)	0·4[a]	NA
Secondary glomerular/systemic disease	–	9 (16·7)	10 (20·4)	0·6[a]	NA
Miscellaneous/unknown	–	14 (25·9)	14 (28·6)	0·8[a]	NA
Medication					
Diuretics	–	12 (22·2)	34 (69·4)	<0·001[a]	NA
ACE inhibitors	–	23 (42·6)	29 (59·2)	0·09[a]	NA
Angiotensin II receptor blockers	–	22 (40·7)	23 (46·9)	0·5[a]	NA
Beta-blockers	–	11 (20·4)	20 (40·8)	0·02[a]	NA
Calcium channel blockers	–	10 (18·5)	28 (57·1)	<0·001[a]	NA

BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; ACE, angiotensin converting enzyme.
Values reported as number (percentage) or mean ± standard deviation.
[a]Chi-square test.
[b]CKD 4–5 versus controls.

Table 2 Echocardiographic variables.

	Controls	CKD 2–3	CKD 4–5	P value ANOVA	P value between groups (*post hoc*)
No. of patients	53	54	49		
Aortic diameter (cm)	2·88 ± 0·33	2·94 ± 0·43	2·82 ± 0·33	0·3	NA
LADs (cm)	3·38 ± 0·48	3·58 ± 0·59	3·64 ± 0·62	0·06	NA
SWTd (cm)	0·99 ± 0·16	1·09 ± 0·20	1·15 ± 0·23	<0·001	<0·001[a] 0·02[b]
LVIDd (cm)	4·71 ± 0·49	4·69 ± 0·60	4·65 ± 0·56	0·9	NA
PWTd (cm)	0·99 ± 0·14	1·02 ± 0·14	1·09 ± 0·19	0·002	0·002[a]
LVM (g)	176·2 ± 44·5	193·4 ± 68·5	207·3 ± 67·6	0·04	0·03[a]
LVMI (g m^{-2})	91·2 ± 17·6	99·7 ± 29·6	107·0 ± 27·2	0·008	0·006[a]
LVH	7 (13)	16 (30)	18 (37)	0·02 (all)[d]	0·006[a] 0·03[b]
RWT (cm)	0·42 ± 0·07	0·46 ± 0·08	0·49 ± 0·10	0·001	<0·001[a]
MWT (cm)	0·99 ± 0·13	1·06 ± 0·16	1·12 ± 0·20	<0·001	<0·001[a]
LV systolic function					
LVEF Teichholz (%)	66·0 ± 8·5	62·5 ± 7·6	62·2 ± 9·6	0·05	0·07[a] 0·09[b]
Septal AV (cm)	1·43 ± 0·22	1·33 ± 0·19	1·31 ± 0·19	0·008	0·01[a] 0·03[b]
Lateral AV (cm)	1·56 ± 0·22	1·47 ± 0·26	1·52 ± 0·30	0·2	NA
Inferior AV (cm)	1·57 ± 0·24	1·44 ± 0·25	1·44 ± 0·23	0·006	0·02[a] 0·01[b]
Anterior AV (cm)	1·43 ± 0·19	1·33 ± 0·25	1·34 ± 0·26	0·05	0·06[b]
Mean AV (cm)	1·50 ± 0·17	1·39 ± 0·20	1·40 ± 0·21	0·008	0·04[a] 0·01[b]
RV systolic function (TAPSE)					
TAPSE (cm)	2·47 ± 0·45	2·31 ± 0·45	2·25 ± 0·40	0·03	0·03[a]
LV diastolic function					
E deceleration time (ms)	206 ± 47	203 ± 40	213 ± 48	0·6	NA
E wave velocity (cm s^{-1})	73 ± 15	74 ± 17	80 ± 18	0·1	NA
A wave velocity (cm s^{-1})	54 ± 13	58 ± 15	69 ± 18	<0·001	<0·001[a] 0·002[c]
E/A	1·43 ± 0·39	1·33 ± 0·35	1·24 ± 0·49	0·09	NA
IVRT (ms)	73·4 ± 17·3	76·6 ± 15·4	77·5 ± 15·5	0·4	NA

LADs, left atrium end-systolic diameter; SWTd, wall thickness of interventricular septum; LVIDd, left ventricular end-diastolic dimension; PWTd, posterior wall thickness; LVM, left ventricular mass; BSA, body surface area; LVMI, left ventricular mass/BSA; LVH, left ventricular hypertrophy; RWT, relative wall thickness; MWT, mean wall thickness; LV, left ventricle; LVEF, left ventricular ejection fraction; AV, atrio-ventricular plane displacement; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; E, early transmitral diastolic flow velocity; A, flow velocity during atrial contraction; IVRT, isovolumic relaxation time.

Values reported as number (percentage) or mean ± standard deviation.

[a]CKD 4–5 versus controls.

[b]CKD 2–3 versus controls.

[c]CKD 4–5 versus CKD 2–3.

[d]Chi-square test.

patients with CKD (CKD 4–5, 62·2 ± 9·6%, P = 0·07; CKD 2–3, 62·5 ± 7·6%, P = 0·09). In addition, the controls had significantly higher longitudinal systolic contraction measured as AV-plane displacement in the septal and inferior LV wall, and also a higher mean value of the four sites of AV-plane displacement (1·50 ± 0·17 cm) compared with the patients with CKD (CKD 4–5, 1·40 ± 0·21 cm, P = 0·04; CKD 2–3, 1·39 ± 0·20 cm, P = 0·01). There were no significant differences between the groups regarding traditional variables of diastolic function such as mitral E velocity, the mitral E/A ratio or the mitral E deceleration time.

In a subgroup analysis of patients with CKD 2–3, there were no significant differences in blood pressure or any echocardiographic variables between subjects with GFR ≥ 60 ml min^{-1} per 1·73 m^2 and GFR <60 ml min^{-1} per 1·73 m^2.

Tissue Doppler imaging variables are summarized in Table 3. The mean value of the systolic TDI velocities of the four sites was significantly higher in controls (11·5 ± 1·9 cm s^{-1}) com-

pared with the CKD groups (CKD 4–5, 10·4 ± 2·1 cm s^{-1}, P = 0·03 and CKD 2–3, 10·4 ± 2·1 cm s^{-1}, P = 0·02).

Controls had a significantly higher septal ϵ' velocity of 13·6 ± 3·0 cm s^{-1} compared with both groups of patients with CKD (CKD 4–5, 11·7 ± 2·8 cm s^{-1}, P = 0·002 and CKD 2–3, 11·8 ± 2·5 cm s^{-1}, P = 0·003). In addition, controls had significantly lower mitral E/ϵ' ratio assessed as the mean E/ϵ' (5·00 ± 1·23) compared with both groups of patients with CKD (CKD 4–5, 6·36 ± 1·71, P<0·001 and CKD 2–3, 5·69 ± 1·47, P = 0·05), indicating impaired diastolic function in the patients with CKD compared with the controls. Septal ϵ'/α' ratio was significantly lower than controls only for CKD 4–5.

Discussion

In this study using tissue Doppler imaging, we found significant abnormalities in diastolic and longitudinal systolic LV function in patients with mild-to-moderate CKD compared
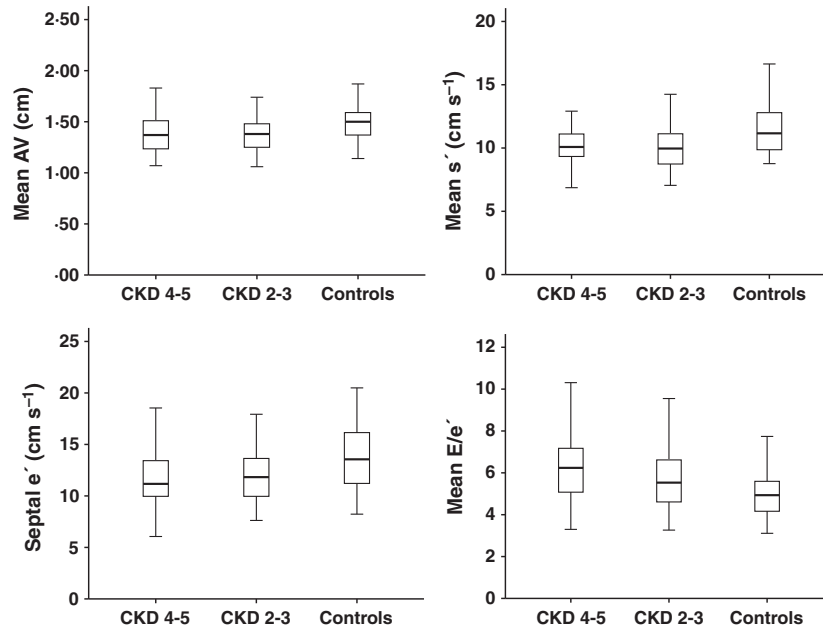
Figure 1 Box plots presenting comparisons of systolic (Mean AV and Mean s′) and diastolic (Septal e′ and Mean E/e′) variables between the CKD groups and controls. Mean AV – mean value of the atrio-ventricular plane displacement of the four sites of the mitral annulus, Mean s′ – mean value of peak systolic myocardial velocities of the four sites of the mitral annulus, Septal e′ – the early diastolic myocardial velocity of the septal part of the mitral annulus, Mean E/e′ – the mean value of the ratio between the velocity of early transmitral diastolic flow velocity (E) and the early diastolic myocardial velocity (e′) of the septal and lateral part of the mitral annulus.

with healthy controls. Both patients with CKD stages 4–5 and those with CKD stages 2–3 showed signs of LV remodelling, with a significantly higher prevalence of LVH than in controls.

In previous studies, increasingly higher LVM has been reported in patients with increasing severity of CKD (Levin et al., 1999; Nardi et al., 2009; Park et al., 2012). In a large cohort of patients with CKD, the prevalence of LVH ranged from 32% in patients with eGFR ≥60 ml min^{-1} per 1·73 m^2 to 75% in patients with eGFR <30 ml min^{-1} per 1·73 m^2 (Park et al., 2012). In our study, we also found an increasing prevalence of LVH in CKD stages 2–3 (30%) and stages 4–5 (37%) compared with controls (13%), at levels similar to those described by others (Levin et al., 1999; Nardi et al., 2009). However, some previous studies have reported an unusually high prevalence of LVH, in up to 78% of patients with CKD stages 3–5 and up to 51% of patients with CKD stages 1–2 (Paoletti et al., 2005). The reasons for this might be suboptimal medical treatment of the studied patient population and the use of different methodology for calculating LVM (Agarwal, 2005). In our study, all the patients were recruited from a dedicated nephrology clinic, which may guarantee better treatment according to current guidelines.

Although large studies have demonstrated changes in LV geometry in patients with CKD, the association between kidney function and impaired global systolic cardiac function has not been clearly established, especially when traditional echocardiographic methods have been used (Park et al., 2012).

Global systolic LV function is traditionally measured as LVEF, calculated from simplistic models using diastolic and systolic dimensions or volumes of the LV (Lang et al., 2005). Recently, the interaction between the complicated structure and orientation of myocardial fibres and the contractile LV function has been clarified (Sengupta et al., 2006). Longitudinal contraction of the left ventricle can be expressed by AV-plane displacement measured by M-mode or/and systolic myocardial velocity measured by TDI. In our study, patients with CKD in both groups had significantly lower systolic myocardial velocities and lower AV-plane displacement, compared with controls. Recent studies employing a newly developed ultrasound-based strain imaging technique confirm our results in terms of impairment of longitudinal systolic function in patients with CKD (Edwards et al., 2008; Liu et al., 2011). We did not find any statistically significant differences between the groups in LVEF calculated by the Teichholz method.

Development of TDI imaging has also influenced the evaluation of diastolic LV function, adding variables calculated from transmitral flow and myocardial velocities. Park et al. (2012) did not find any graded association between kidney function and diastolic LV function assessed by traditional methods. However, they did not use TDI for the assessment of diastolic function and they did not have a healthy control group for comparison. In our study, we did not see any significant differences between the groups regarding traditional characteristics of transmitral inflow pattern (E/A ratio) or left atrial

Table 3 Tissue Doppler imaging.

	Controls	CKD 2–3	CKD 4–5	P value ANOVA	P value between groups (post hoc)
No. of patients	53	54	49		
Septal s' (cm s^{-1})	9·4 ± 1·2	8·9 ± 1·3	9·1 ± 1·6	0·2	NA
Septal e' (cm s^{-1})	13·6 ± 3·0	11·8 ± 2·5	11·7 ± 2·8	0·001	0·002[a] 0·003[b]
Septal a' (cm s^{-1})	11·9 ± 2·1	11·4 ± 1·6	13·1 ± 3·1	0·001	0·001[c] 0·02[a]
Septal $e'a'$ ratio	1·21 ± 0·45	1·06 ± 0·30	0·936 ± 0·31	0·001	0·001[a]
Lateral s' (cm s^{-1})	12·4 ± 2·8	11·2 ± 3·7	10·7 ± 2·9	0·02	0·02[a]
Lateral e' (cm s^{-1})	17·6 ± 4·9	15·6 ± 4·5	15·0 ± 4·9	0·02	0·02[a]
Lateral a' (cm s^{-1})	11·7 ± 2·8	11·5 ± 3·3	12·0 ± 3·0	0·7	NA
Lateral $e'a'$ ratio	1·63 ± 0·77	1·44 ± 0·52	1·35 ± 0·64	0·09	NA
Mean $e'a'$ ratio	1·42 ± 0·57	1·25 ± 0·36	1·14 ± 0·45	0·01	0·01[a]
Inferior s' (cm s^{-1})	10·9 ± 1·6	10·2 ± 1·3	10·2 ± 1·7	0·02	0·04[a] 0·05[b]
Inferior e' (cm s^{-1})	15·4 ± 3·8	14·3 ± 3·6	13·6 ± 4·5	0·07	NA
Inferior a' (cm s^{-1})	13·1 ± 2·2	12·3 ± 2·2	13·6 ± 3·7	0·06	NA
Anterior s' (cm s^{-1})	13·2 ± 5·1	11·2 ± 4·0	11·6 ± 4·2	0·07	NA
Anterior e' (cm s^{-1})	17·5 ± 5·0	15·4 ± 5·2	14·3 ± 4·0	0·003	0·003[a]
Anterior a' (cm s^{-1})	12·9 ± 5·6	11·3 ± 3·1	12·6 ± 4·0	0·2	NA
Mean s' (cm s^{-1})	11·5 ± 1·9	10·4 ± 2·1	10·4 ± 2·1	0·01	0·03[a] 0·02[b]
E/e' sept	5·59 ± 1·38	6·39 ± 1·64	7·12 ± 2·26	<0·001	<0·001[a]
E/e' lat	4·41 ± 1·26	4·99 ± 1·62	5·60 ± 1·55	0·001	<0·001[a]
Mean E/e'	5·00 ± 1·23	5·69 ± 1·47	6·36 ± 1·71	<0·001	<0·001[a] 0·05[b]

s', peak systolic myocardial velocity; e', early diastolic myocardial velocity; a', late diastolic myocardial velocity; mean s', mean value of peak systolic myocardial velocity of the septal, lateral, inferior and anterior part of the mitral annulus; E, early transmitral diastolic flow velocity; sept, septal part of the mitral annulus; lat, lateral part of the mitral annulus; mean E/e', mean value of E/e' sept and E/e' lat.
Values reported as number or mean ± standard deviation.
[a]CKD 4–5 versus controls.
[b]CKD 2–3 versus controls.
[c]CKD 4–5 versus CKD 2–3.

size. However, when TDI was used, the patients with CKD in both groups had significantly lower septal diastolic velocity (e') and higher mitral mean E/e' ratio compared with the controls, indicating an impairment of diastolic function in the patients with CKD, although the majority had preserved LVEF. These changes in diastolic variables may be precursors of clinical heart failure. Devereux et al. (2000) showed that the patients with renal dysfunction are more likely to have heart failure with preserved LVEF. Our findings are consistent with previous studies showing that TDI is a more sensitive tool than conventional echocardiography for the detection of impaired diastolic function in the patients with CKD (Hayashi et al., 2006; de Almeida et al., 2007).

There are some study limitations. The sample size is relatively small. We were not able to ascertain the duration of comorbid conditions, such as hypertension and diabetes.

Conclusion

Alterations in systolic and diastolic myocardial function, compared with healthy subjects, can be seen in patients with even mild-to-moderate CKD when TDI is used. Traditional echocardiographic measures of diastolic function did not show any significant differences. There was also an increasing prevalence of LVH with increasing severity of CKD. Our findings indicate that cardiac involvement is already present in mild-to-moderate CKD and may be a precursor of premature cardiac morbidity.

Conflict of interest

The authors declare no conflict of interest.

References

Agarwal R. Prevalence of left ventricular hypertrophy: some alternate thoughts. *Am J Kidney Dis* (2005); **46**: 1148;1148–1149.

de Almeida EA, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Diastolic function in several stages of chronic kidney disease in patients with autosomal dominant polycystic kidney disease: a tissue Doppler imaging study. *Kidney Blood Press Res* (2007); **30**: 234–239.

Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* (2004); **351**: 1285–1295.

Chen SC, Su HM, Hung CC, Chang JM, Liu WC, Tsai JC, Lin MY, Hwang SJ, Chen HC. Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease. *Clin J Am Soc Nephrol* (2011); **6**: 2750–2758.

Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* (1999); **56**: 2214–2219.

Derumeaux G, Mulder P, Richard V, Chagraoui A, Nafeh C, Bauer F, Henry JP, Thuillez C. Tissue Doppler imaging differentiates physiological from pathological pressure-overload left ventricular hypertrophy in rats. *Circulation* (2002); **105**: 1602–1608.

Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* (1986); **57**: 450–458.

Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. *Am J Cardiol* (2000); **86**: 1090–1096.

Dogan U, Ozdemir K, Akilli H, Aribas A, Turk S. Evaluation of echocardiographic indices for the prediction of major adverse events during long-term follow-up in chronic hemodialysis patients with normal left ventricular ejection fraction. *Eur Rev Med Pharmacol Sci* (2012); **16**: 316–324.

Edwards NC, Hirth A, Ferro CJ, Townend JN, Steeds RP. Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: the precursor of uremic cardiomyopathy? *J Am Soc Echocardiogr* (2008); **21**: 1293–1298.

Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* (1995); **47**: 186–192.

Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* (1998); **32**(Suppl 3): S112–S119.

Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* (2003); **41**: 1364–1372.

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* (2004); **351**: 1296–1305.

Gulel O, Soylu K, Yuksel S, Karaoglanoglu M, Cengiz K, Dilek M, Hamiseyev C, Kale A, Arik N. Evidence of left ventricular systolic and diastolic dysfunction by color tissue Doppler imaging despite normal ejection fraction in patients on chronic hemodialysis program. *Echocardiography* (2008); **25**: 569–574.

Hayashi SY, Rohani M, Lindholm B, Brodin LA, Lind B, Barany P, Alvestrand A, Seeberger A. Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. *Nephrol Dial Transplant* (2006); **21**: 125–132.

Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney Int* (2002); **62**: 1402–1407.

Henry RM, Kamp O, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD. Mild renal insufficiency is associated with increased left ventricular mass in men, but not in women: an arterial stiffness-related phenomenon–the Hoorn Study. *Kidney Int* (2005); **68**: 673–679.

Höglund C, Alam M, Thorstrand C. Atrioventricular valve plane displacement in healthy persons. An echocardiographic study. *Acta Med Scand* (1988); **224**: 557–562.

Hosseinpanah F, Barzin M, Golkashani HA, Nassiri AA, Sheikholeslami F, Azizi F. Association between moderate renal insufficiency and cardiovascular events in a general population: Tehran lipid and glucose study. *BMC Nephrol* (2012); **13**: 59.

Hung MJ, Yang NI, Wu IW, Cheng CW, Wu MS, Cherng WJ. Echocardiographic assessment of structural and functional cardiac remodeling in patients with predialysis chronic kidney disease. *Echocardiography* (2010); **27**: 621–629.

Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* (2007); **18**: 1307–1315.

Krutzén E, Bäck SE, Nilsson-Ehle I, Nilsson-Ehle P. Plasma clearance of a new contrast agent, iohexol: a method for the assessment of glomerular filtration rate. *J Lab Clin Med* (1984); **104**: 955–961.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* (2005); **18**: 1440–1463.

Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* (1999); **34**: 125–134.

Liu YW, Su CT, Huang YY, Yang CS, Huang JW, Yang MT, Chen JH, Tsai WC. Left ventricular systolic strain in chronic kidney disease and hemodialysis patients. *Am J Nephrol* (2011); **33**: 84–90.

Matsumoto M, Io H, Furukawa M, Okumura K, Masuda A, Seto T, Takagi M, Sato M, Nagahama L, Omote K, Hisada A, Horikoshi S, Tomino Y. Risk factors associated with increased left ventricular mass index in chronic kidney disease patients evaluated using echocardiography. *J Nephrol* (2012); **25**: 794–801.

Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. *J Am Soc Nephrol* (2001); **12**: 1079–1084.

Nardi E, Palermo A, Mulè G, Cusimano P, Cottone S, Cerasola G. Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertens* (2009); **27**: 633–641.

National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* (2002); **39**(Suppl 1): S1–S266.

Paoletti E, Bellino D, Cassottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis CKD. *Am J Kidney Dis* (2005); **46**: 320–327.

Paoletti E, Bellino D, Gallina AM, Amidone M, Cassottana P, Cannella G. Is left ventricular hypertrophy a powerful predictor of progression to dialysis in chronic kidney disease? *Nephrol Dial Transplant* (2011); **26**: 670–677.

Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J, Anderson A, Go AS, Shlipak MG, Chronic Renal Insufficiency Cohort (CRIC) Study Group. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* (2012); **23**: 1725–1734.

Rakhit DJ, Zhang XH, Leano R, Armstrong KA, Isbel NM, Marwick TH. Prognostic role of subclinical left ventricular abnormalities and impact of transplantation in chronic kidney disease. *Am Heart J* (2007); **153**: 656–664.

Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A, Khandheria BK. Left ventricular structure and function: basic science for cardiac imaging. *J Am Coll Cardiol* (2006); **48**: 1988–2001.

Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* (1976); **37**: 7–11.

Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. *Am J Cardiol* (2001); **88**: 53–58.

Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Stancanelli B, Cataliotti A, Malatino LS. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int* (2004a); **65**: 1492–1498.

Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Cataliotti A, Seminara G, Stancanelli B, Malatino LS. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. *J Am Soc Nephrol* (2004b); **15**: 1029–1037.